CLINICAL REPORT

Panniculitis due to Non-Tuberculous Mycobacteria in Two Immunocompromised Patients

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Inflammation of subcutaneous tissue (panniculitis) may occur in association with tuberculosis, but so far only three cases of non-tuberculous mycobacteria-related lobular panniculitis have been reported. We describe two new cases with marked cellular immunity failure due to hypercorticism. Clinical presentation did not differ significantly from lobular panniculitis of other aetiologies. Histological samples displayed signs of lobular panniculitis and clues for mycobacteria infection with granulomatous lesions and presence of numerous acid-fast bacilli on special staining. Both patients responded quickly to a combination of macrolides, ethambutol and fluoroquinolones. However, like in other infections with tuberculous or non-tuberculous mycobacteria, long-term treatment (at least 6 months) was necessary to prevent relapses.

Non-tuberculous mycobacteria (NTM) are widely distributed microorganisms responsible for cutaneous and visceral infections which often occur in patients displaying cellular immune response impairment. Clinical presentation of cutaneous infections by NTM is variable depending on the type of mycobacteria involved, but the most common pattern is probably deep skin abscesses. Non-abscessed infectious lobular panniculitis due to NTM has been very rarely reported to date and seems to be of uncertain prognosis. We hereby describe two new cases occurring in immuno-suppressed, non-HIV-infected patients.

CASE REPORTS

Case 1

A 55-year-old man was referred for diffuse cutaneous lesions of at least 3 months duration. His previous medical history was unremarkable except for a severe steroid-dependent asthma and a steroid-related, non-insulin-dependent diabetes mellitus. He had been receiving oral high-dose prednisone (0.5–1 mg/kg/day; 0.5 mg/kg/day at the time of referral) for more than 20 years. Initial physical examination revealed widespread deep inflammatory cutaneous nodules located on his left arm and both lower limbs (Fig. 1) along with various skin lesions related to long-term steroid treatment (atrophy, purpura, star-like pseudo-scars). His general condition was otherwise good. He denied any weight loss or fever. Two skin biopsy specimens from different affected sites revealed a lobular panniculitis mainly consisting of granulomatous inflammatory infiltrates composed of histiocytes and multinucleate giant cells but without any feature of abscess. Ziehl-Nielsen staining was positive with numerous acid-fast bacilli scattered throughout the infiltrates. Cultures on mycobacteria-specific medium were also positive in two different laboratories including a national reference laboratory (Institut Pasteur, Paris) within 9–12 days, but no precise identification of the NTM subgroup could be achieved. The tuberculosis skin test was negative and immunophenotyping of peripheral blood lymphocytes disclosed a mildly decreased CD4+ T-cell count down to 400/mm^3 (CD4/CD8 = 0.4; normal range 1–2.3) without HIV infection. Other investigations including chest tomo-densitometry and culture of urine, sputum and blood were negative except for the isolation of *Mycobacterium xenopi* in sputum. No antibiogram was performed. The patient received clarithromycin (1500 mg/day) and

Fig. 1. Cutaneous inflammatory, non-abscessed nodules on right lower limb.

doxycycline (200 mg/day) for 8 months. This treatment was well tolerated and fully efficient within 3 months, despite the continuation of steroid therapy and there was no sign of recurrence after a follow-up of >6 months after treatment was stopped.

Case 2

A 78-year-old woman without a remarkable medical history was admitted for investigation of protracted asthenia, weight loss, diabetes mellitus of recent onset associated with skin lesions and morphological changes consistent with Cushing's syndrome. Cutaneous examination disclosed painful confluent nodules of both lower limbs, some of them giving rise to fistulae and discharging a yellowish pus. There was a localized inflammatory oedema of both halluces. Several biopsy specimens from the nodules consistently showed a lobular panniculitis with acute inflammatory infiltrates mainly composed of neutrophils, very rare granulomatous features without any true pattern of abcess and the presence of numerous acid-fast bacilli by Ziehl-Nielsen staining (Fig. 2). A strain of *M. chelonae* grew from both tissue sample from cutaneous inflammatory nodules and pus in less than a week. No antibiogram was performed. The tuberculosis skin test was negative and immunophenotyping of peripheral blood lymphocytes disclosed a strongly decreased CD4+ T-cell count down to 164/mm^3 (CD4/CD8=0.2) without HIV infection. Biological tests and morphological investigations confirmed Cushing's syndrome related to a macroscopic pituitary adenoma. Chest tomodensitometry was normal and bacteriological cultures of urine, sputum and blood were negative. The adenoma was surgically removed with full success and the patient received ethambutol (800 mg/day), ofloxacin (400 mg/day) and clarithromycin (1800 mg/day). This treatment was fully efficient with considerable clinical improvement along with negative skin cultures after 3 months
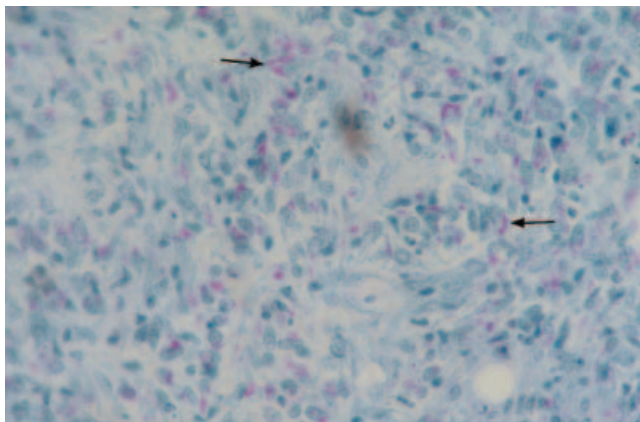

Fig. 2. Inflammatory infiltrates with predominance of neutrophils and presence of acid-fast bacilli (arrows) on Ziehl-Nielsen staining (original magnification × 250).

and the antibiotics were interrupted. However, the lesions relapsed 1 month after antibiotics were stopped. A second course combining ofloxacin (400 mg/day) and clarithromycin (1500 mg/day) was implemented with a marked clinical improvement, although a complete clearance of lesions could not be achieved. Indeed, the cutaneous elements were still slightly active after 1 year of continuous treatment and a cutaneous biopsy showed an inflammatory, histiocyte-rich infiltrate, although both Ziehl-Nielsen staining and skin lesion culture for *Mycobacterium* gave negative results.

DISCUSSION

Lobular panniculitis (LP) is an inflammatory process primarily affecting cutaneous fat lobules which can be related to a number of aetiologies including pancreatic disorders, systemic diseases, physical agents and specific infections. Numerous microorganisms can be responsible for infectious LP, such as *Brucella melitensis* (1), *Toxoplasma gondii* (2), *Histoplasma, Nocardia* (3), *Candida albicans* (3, 4), and *Fusarium* species (3). Cases of LP directly related to mycobacteria infections seem very unusual, with only three well-documented observations in the international literature to date (5–7). Moreover, two large nationwide retrospective studies reporting on NTM-related cutaneous lesions did not include any cases of LP (8, 9). As regards the species of the responsible mycobacteria, the three previously reported cases (5–7) involved *M. avium intracellulare* (5), *M. chelonae* (6) and *M. fortuitum* (7). *M. chelonae* was found in our second patient. No clear identification by a reference laboratory could be made for our first patient, although the diagnosis of mycobacteria-related LP seems to be established on safe grounds according to cumulative evidence of special staining, repeated positive skin cultures before treatment and good efficiency of treatment, evidence that makes a non-specific, circumstantial presence of a NTM in inflammatory lesions of other origin very unlikely. The isolation of *M. xenopi* from sputum is not a definite clue as to the involved strain since this bacteria is often present in immunocompromised patients' lungs without any clear pathogenic role. It may be hypothesized that this infection was due to an unusual, opportunistic strain whose identification cannot be easily performed on a routine basis.

It is of interest to point out that all reported cases, including our two patients, had a background of hypercorticism (either iatrogenic or intrinsic), usually of long duration, making it likely that cellular immunodeficiency is a common feature and a major risk factor in such infections. This deficiency was clearly documented in both our patients with a low CD4+ T-cell count and negative tuberculosis skin test.

Overall, the five observations display a consistent, non-specific clinical presentation which usually consists

of inflammatory, sometimes confluent nodules of the limbs. Lower limbs are most often involved but upper limbs may also be affected as shown by our first patient. Local inflammation is variable and can be deceptively slight, which may partly account for the usually long delay before an accurate diagnosis is made (mean 8 months). Fistulization with discharge is possible as illustrated by our second patient but remains unusual. It is of crucial importance to systematically search for visceral involvement in NTM-related LP especially in lungs, although only one patient among the previously published cases showed visceral manifestations (5). In our patients, no extracutaneous spreading was present apart from the doubtful presence of *M. xenopi* in sputum in our first patient. General status is not markedly altered by the infection itself, but may be impaired by the underlying pathological condition as illustrated by our second patient who was in poor general condition due to Cushing's syndrome.

As to histological findings, all three published cases reported a granulomatous LP with giant multinucleate cells and, except for one patient who had received a prior antibiotherapy (6), acid-fast bacilli could be identified on the biopsy specimen with Ziehl-Nielsen-specific coloration which implies a high bacterial burden. Furthermore, an acute inflammatory infiltrate composed of neutrophils was present in two of the three reported cases (6, 7), a feature considered by some authors (3) as a major histological criterion in favour of the infectious origin of LP. Epidermal changes (acanthosis, parakeratosis) and a secondary involvement of hypodermic septa could also draw attention toward an infectious aetiology of LP but their value is more questionable (3). Overall, our observations are in line with these data, especially regarding the abundant neutrophilic infiltrate displayed by our second patient.

Treatment of skin NTM infections in general and of mycobacteria-related infectious LP in particular is often difficult, perhaps because they often occur in patients with impaired cellular immunity. NTM infections are frequently refractory to usual anti-tuberculosis drugs; imipenem, ethambutol, macrolides (especially clarithromycin) (10, 11) along with fluoroquinolones (12, 13) are currently the most widely used antibiotics. Accordingly, it is highly recommended that a suitable antibiogram is performed, although a significant result is often difficult to obtain for technical reasons. To date there is no real consensus, but a combination of two antibiotics for at least 6 months appears to be necessary. The recurrence and the more protracted course of the disease in our second patient is probably due to a shorter treatment period and to a deeper alteration of cellular immunity as featured by a low peripheral T-cell count. The simultaneous use of multiple antibiotics might help to decrease the emergence of NTM resistance, already described with clarithromycin (14) or fluoroquinolones

(12) when used alone. Lastly, our second patient illustrates the possibility that a protracted treatment, perhaps lifelong in some cases, may be necessary to avoid a relapse of lesions when a cellular immune deficiency is still present and does not allow for a definitive cure of the disease in spite of the antibiotic treatment.

REFERENCES

1. Bartralot R, Garcia-Patos V, Repiso T, Alegre J, Fernandez de Sevilla T, Marques A, et al. Liquefactive panniculitis in the inguinal area as the first sign of chronic renal brucellosis. J Am Acad Dermatol 1996; 35: 339–341.
2. Arnold SJ, Kinney MC, McCormick MS, Dummer S, Scott M. Disseminated toxoplasmosis. Unusual presentations in the immunocompromised host. Arch Pathol Lab Med 1997; 121: 869–873.
3. Patterson JW, Brown PC, Broecker AH. Infection-induced panniculitis. J Cutan Pathol 1989; 16: 183–193.
4. Ginter G, Rieger E, Soyer HP, Hoedl S. Granulomatous panniculitis caused by *Candida albicans*: a case presenting with multiple leg ulcers. J Am Acad Dermatol 1993; 28: 315–317.
5. Sanderson TL, Moskowitz L, Hensley GT, Cleary TJ, Penneys N. Disseminated *Mycobacterium avium-intracellulare* infection appearing as a panniculitis. Arch Pathol Lab Med 1982; 106: 112–114.
6. Bendelac A, Cambazard F, Fougerat J, Forestier JY, Thivolet J. Infections cutanées à *Mycobacterium chelonei*. Revue générale à propos d'un cas. Ann Dermatol Venereol 1985; 112: 319–324.
7. Retief CR, Tharp MD. *Mycobacterium fortuitum* panniculitis in a steroid-dependent asthmatic patient. J Am Acad Dermatol 1998; 39: 650–653.
8. Street ML, Umbert-Millet IJ, Roberts GD, Su WP. Nontuberculous mycobacterial infections of the skin. Report of fourteen cases and review of the literature. J Am Acad Dermatol 1991; 24: 208–215.
9. Bonafe JL, Grigorieff-Larrue N, Bauriaud R. Les mycobactérioses cutanées atypiques. Resultats d'une enquête nationale. Ann Dermatol Venereol 1992; 119: 463–470.
10. Brown BA, Wallace RJ Jr, Onyi GO, De Rosas V, Wallace RJ 3rd. Activities of four macrolides, including clarithromycin, against *Mycobacterium fortuitum*, *Mycobacterium chelonae*, and *M. chelonae*-like organisms. Antimicrob Agents Chemother 1992; 36: 180–184.
11. Brown BA, Wallace RJ Jr, Onyi GO. Activities of clarithromycin against eight slowly growing species of nontuberculous mycobacteria, determined by using a broth microdilution MIC system. Antimicrob Agents Chemother 1992; 36: 1987–1990.
12. Wallace RJ Jr, Bedsole G, Sumter G, Sanders CV, Steele LC, Brown BA, et al. Activities of ciprofloxacin and ofloxacin against rapidly growing mycobacteria with demonstration of acquired resistance following single-drug therapy. Antimicrob Agents Chemother 1990; 34: 65–70.
13. Young LS, Berlin OG, Inderlied CB. Activity of ciprofloxacin and other fluorinated quinolones against mycobacteria. Am J Med 1987; 82: 23–26.
14. Ji B, Lounis N, Truffot-Pernot C, Grosset J. Selection of resistant mutants of *Mycobacterium avium* in beige mice by clarithromycin monotherapy. Antimicrob Agents Chemother 1992; 36: 2839–2842.